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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/196,867 | 11/20/98 | KELSALL | B 14014.0312 |

HM12/0120

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| EXAMINER | |
|---|---|
| DECLOUX, A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | 9 |

**DATE MAILED:** 01/20/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/196,867 | Kelsall et al |
| **Examiner** | **Group Art Unit** |
| DeCloux, Amy | 1644 |

☒ Responsive to communication(s) filed on *Nov 16, 1999* .

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-13* is/are pending in the application.

Of the above, claim(s) *9 and 11-13* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8 and 10* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. Applicant's amendment, filed 11/16/99 (Paper No. 8), is acknowledged.
Claims 1-13 are pending.
Claims 1-8, and 10 are being examined presently.

2. Applicant's election with traverse of Group I (Claims 1-11) in Applicant's amendment, filed 11/16/99 (Paper No. 8), is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to examine the claims of Groups II and III concurrently. This is not found persuasive because of the reasons of record show these inventions to be patentably distinct. While the searches of these inventions may overlap, there is no reason to expect the searches to be coextensive. Accordingly, serious search burden exists. Furthermore, different considerations are required under 112 for different diseases.

The requirement is still deemed proper and is FINAL.

3. Claims 12 and 13 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Applicant's amendment, filed 11/16/99, (Paper No. 8).
Claims 9 and 11 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species, the requirement having been traversed in Applicant's amendment, filed 11/16/99, (Paper No. 8).

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: It does not state that the person making the oath or declaration believes the named inventor or inventors to be the original and first inventor or inventors of the subject matter which is claimed and for which a patent is sought. It is noted that Page 1 of the three page oath appears to be missing.

5. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5, 6, 7, 8, and 10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating the interleukin-12-induced inflammatory response of inflammatory bowel disease comprising administering a ligand of complement receptor 3, does not reasonably provide enablement for preventing the interleukin-12-induced inflammatory response of inflammatory bowel disease or of any other TH-1 cell mediated autoimmune disease, comprising administering a ligand of complement receptor 3. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to use the claimed methods commensurate in scope with the instant claims.

There is insufficient evidence that the claimed methods comprising administering a ligand of complement receptor 3 to prevent the interleukin-12-induced inflammatory response of inflammatory bowel disease or of any other TH-1 cell mediated autoimmune disease recited in Claims 5, 6, 7, 8, and 10, can actually prevent the interleukin-12-induced inflammatory response of inflammatory bowel disease or of any other TH-1 cell mediated autoimmune disease. The prevention of the interleukin-12-induced inflammatory response of an inflammatory bowel disease such as Crohn's disease, for example, is unpredictable because it is not clear what causes the immune phenomena including the induction of IL-12 that is believed to play a key role in the pathogenesis of Crohn's disease as indicated by Pallone et al (Gut 43:735-6, 1998)(see entire article especially the last paragraph of column 2 on page 735 and the first paragraph on page 736). The prevention of the interleukin-12-induced inflammatory response of any other TH-1 cell mediated autoimmune disease is also unpredictable because it is not clear what causes the immune phenomena including the induction of IL-12 involved in the pathogenesis of other TH-1 cell mediated autoimmune disease as indicated by Marth et al ( as indicated on page 1993, column 2 lines 1-4 J. Exp. Med. 185:1987-1995, June 2, 1997). Therefore, given the lack of knowledge of what causes the IL-12 induced inflammatory response of Crohn's disease, or of any other TH-1 cell mediated autoimmune disease, there is insufficient evidence provided in the instant specification that the claimed methods would prevent said response to Crohn's disease, or to any other TH-1 cell mediated autoimmune disease, without undue experimentation.

In view of the quantity of experimentation necessary, the limited working examples of prevention of the IL-12 induced inflammatory response of Crohn's disease, or of any other TH-1 cell mediated autoimmune disease using the claimed methods, the unpredictability of the art, and the lack of sufficient guidance in the specification in terms of prevention as opposed to treatment of the IL-12 induced inflammatory response of inflammatory bowel diseases such as Crohn's disease, or of any other TH-1 cell mediated autoimmune disease, it would take undue trials and errors to practice the claimed invention with a reasonable expectation that the claimed methods are effective for the prevention of the IL-12 induced inflammatory response of an inflammatory bowel disease or of any other TH-1 cell mediated autoimmune disease, and this is not sanctioned by the statute.

7. Claims 7, 8, and 10 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Claims 7, 8 and 10 are drawn to a method of treating or preventing the interleukin -12-induced inflammatory response of an inflammatory bowel disease with a ligand of complement receptor 3 in a human subject. However, the specification does not enable one of skill in the art regarding the efficacy of said treatment in humans. The efficacy of said treatment methods in the rodent models of inflammatory bowel disease disclosed in the specification may not correlate well with the efficacy of said treatment methods in humans, since it is not known the extent to which these rodent models represent true human inflammatory bowel disease (See Duchmann et al. Eur. J. Immunol. 26:934-938, 1996, especially page 934, column 2, lines 12-16). Therefore, it is not clear that the skilled artisan could predict the efficacy of said treatment methods exemplified in the specification to human subjects, as encompassed by the claims 7, 8 and 10.

In view of the quantity of experimentation necessary, the limited working examples of treatment and prevention of inflammatory bowel disease in humans using the claimed methods, the unpredictability of the art, and the lack of sufficient guidance in the specification in terms of treatment and prevention of inflammatory bowel diseases such as Crohn's disease in humans encompassed by the instant claims, it would take undue trials and errors to practice the claimed invention with a reasonable expectation that the claimed methods are effective for the treatment and prevention of inflammatory bowel disease in human, and this is not sanctioned by the statute.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-2 are rejected under 35 U.S.C. § 102(a) as being anticipated by Marth et al. (J. Exp. Med. 185:1987-1995, June 2, 1997).

Marth et al teach a method of suppressing IL-12 production and it's associated inflammatory response (as shown by the suppression of IFN-gamma production) in a murine model of septic shock by treatment with CR3 antibodies (see entire article, especially Figure 7). Therefore, the referenced teachings anticipate the claimed invention.

11. Claims 1-8 and 10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Marth et al. (J. Exp. Med. 185:1987-1995, June 2, 1997) in view of Neurath et al (J. Exp. Med. 182:1281-1290, 1995) and Duchmann et al. (Eur. J. Immunol. 26:934-938, 1996).

Marth et al. teach as described above, and also teach the ability of antibodies to CR3 to ameliorate Th1 cell mediated autoimmune diseases (see entire article, especially page 1993, column 2, first paragraph). However, Marth et al do not specifically teach a method of reducing the symptoms of autoimmune diseases such as the inflammatory bowel disease of Crohn's disease in humans using ligands to CR-3 such as antibodies to CR-3.

Neurath et al. teaches the method of administration of antibodies against IL-12 which resulted in the abrogation of the colitis induced by TNBS in a murine model of chronic intestinal inflammation with symptoms including weight loss, and mimics some characteristics of Crohn's disease in humans (see entire article, especially the abstract,) and that the inflammation induced by TNBS is associated with a TH-1 response and can be abrogated by systemic treatment with antibodies against IL-12 (see entire article, especially page 1288). Neurath et al. also teaches that IL-12 has pleiotropic effects, plays a pivotal role in driving the TH 1 response and can be efficiently induced by bacteria and bacterial products (see entire article, especially page 1281, columns 1 and 2).

Duchmann et al teach that the pathogenesis of inflammatory bowel disease is due to the hyperresponsiveness to intestinal flora (See entire article, especially the abstract and page 934, column 2).

Therefore, one of ordinary skill in the art at the time the invention was made, who wanted to treat the symptoms of an autoimmune inflammatory disease such as Crohn's disease, would have been motivated to substitute the anti-CR3 antibodies as taught by Marth et al. for the antibodies against IL-12, in a method to down regulate IL-12 production in order to reduce an IL-12 inflammatory response and to abrogate the IL-12 mediated symptoms of an autoimmune disease such as inflammatory bowel disease taught by Neurath et al, especially given the success of anti-CR3 antibodies in down regulating IL-12 and its associated inflammation in an animal model of septic shock as taught by Marth et al, because the anti-CR3 antibodies down regulate IL-12 at its source in a more specific manner than anti- IL-12 antibodies. Since the pathogenesis of autoimmune inflammatory disease may be a result of hyperresponsiveness to intestinal flora taught by Duchmann, this increased specificity of anti-CR3 antibodies relative to anti-IL-12 antibodies is due to the ability of the anti-

CR3 antibodies to abrogate the initial response derived from CR-3 recognition of bacterial substances by phagocytes, and stem the resulting secretion of IL-12 at its cellular source, rather than to sequester the IL-12 once it has been produced.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy DeCloux whose telephone number is (703) 306-5821. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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January 18, 2000

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